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Abstract

Introduction

A standardized histologic definition and classification of patterns of renal tumor pseudocapsular invasion (RTPI) in renal cell carcinoma (RCC) is not available. The aim of the present study was to propose a classification of RTPI patterns and assess their correlation with other pathologic features and prognosis.

Patients and Methods

The renal tumor pseudocapsule was assessed by 2 expert genitourinary pathologists on the histologic slides of 190 specimens from radical nephrectomy performed for organ-confined (pT1-pT2) RCC. The histologic patterns of RTPI were classified and described. The association between the RTPI patterns and other pathologic features was assessed. The Kaplan-Meier method was used to calculate the survival functions, and Cox regression models were used to assess the predictors of cancer-specific survival.

Results

RTPI was classified into 2 main histologic patterns (expansive and infiltrative). Expansive and infiltrative RTPI was observed in 39.5% and 51.6% of cases, respectively. A significant association between the RTPI pattern and Fuhrman grade ($P = .006$) and RCC histologic subtype ($P = .034$) was detected. Patients with infiltrative pseudocapsular invasion had significantly poorer 5- and 10-year cancer-specific survival rates than patients with expansive invasion or no invasion (93.6% vs. 98.9% and 84.9% vs. 93%, respectively; $P = .039$). The presence of infiltrative

pseudocapsular invasion was a significant predictor of cancer-specific survival (hazard ratio 4.38, 95% confidence interval 1.04-20.27).

Conclusion

An expansive and an infiltrative RTPI pattern can be described. In our study, patients with organ-confined RCC and an infiltrative RTPI pattern had a greater risk of cancer-specific death and might require stricter postoperative surveillance strategies.

Introduction

The incidence of renal cell carcinoma (RCC) has been increasing in the past decades.1 Although most RCCs are organ confined at diagnosis, about 20% of patients undergoing nephrectomy will progress to metastatic disease during the follow-up period. In the past few years, the identification of the predictors of tumor progression after surgery has become important to allow tailoring follow-up strategies and select patients for adjuvant treatment in clinical trials. TNM stage and Fuhrman grade are known as the most powerful prognostic factors of cancer-specific survival (CSS) after surgical treatment of RCC.2-4 Other histologic characteristics have been studied for their prognostic impact, including tumor histologic subtype, coagulative necrosis, microvascular invasion, sarcomatoid differentiation, and invasion of the renal capsule on the perinephric side.5,6 In contrast, limited information is available on the prognostic role of tumor invasion of the fibrous pseudocapsule that completely surrounds renal neoplasms.7,8 Different histologic variants of renal tumor pseudocapsular invasion (RTPI) have been observed, which might potentially predict different biologic and clinical behavior of RCC. However, a standardized histologic definition and classification of RTPI patterns is not currently available. In the present study, we reviewed the pathologic slides and the clinical information from a consecutive cohort of patients who had undergone radical nephrectomy (RN) for organ-confined RCC with the aim of describing and classifying the histologic patterns of RTPI and evaluating their correlation with other histologic features and prognosis.

Patients and Methods

Study Population We retrospectively reviewed the records of 308 patients who had undergone open or laparoscopic RN at 2 academic centers from January 2000 to April 2010. Patients with organ-confined (pT1- pT2), pathologically confirmed RCC according to the 2002 American Joint Committee on Cancer (AJCC) TNM classification were considered eligible for the present study.9 Patients were excluded if the histologic slides were missing, lost, or not suitable for pathologic review. The histologic material was considered insufficient when < 3 slides with tumor

surrounded by the pseudocapsule were available. When the tumor size was < 25 mm, < 3 slides were considered sufficient if the whole lesion was included in the slide. Patients were not eligible if the pathologic revision identified a benign tumor, venous invasion, or infiltration of the perinephric or sinus fat, Gerota fascia, adrenal gland, regional lymph nodes, or surrounding organs. All patients preoperatively underwent chest radiography and abdominal computed tomography (CT). Patients with evidence of distant metastatic disease at diagnosis were excluded. The oncologic follow-up protocol included abdominal imaging (CT scan or ultrasonography) and chest radiography every 6 months for 3 years and yearly thereafter. Overall, 190 patients were considered eligible for the study and included in the analysis. The study was performed in accordance with the principles of the Declaration of Helsinki. For each patient, the demographic, clinical, and pathologic data were collected into a dedicated database. Pathologic Assessment At nephrectomy, all specimens were fixed in 4% formaldehyde, and representative tumor fragments were embedded in paraffin and stained according to standard methods (hematoxylin-eosin). Two expert genitourinary pathologists (E.B., C.B.) reviewed all pathologic specimens. The following traditional histologic variables were assessed: histologic subtype according to the World Health Organization 2004 classification,10 tumor grade according to the Fuhrman classification,11 presence of intratumoral necrosis, and presence of sarcomatoid differentiation. When the results were not concordant, the 2 reviewers reached a consensus after further examination of the slides. The tumor pseudocapsule was thoroughly evaluated in all cases and the presence of RTPI assessed. After collegial discussion, a classification of RTPI patterns was defined, and the histologic features of the different variants were carefully described. Statistical Analysis The association between RTPI and the available clinical and pathologic features was assessed using the c2 , Fisher's exact, and Kruskal-Wallis tests for categorical and continuous variables, as appropriate. For this purpose, RTPI was classified into 3 groups: no RTPI, expansive RTPI, and infiltrative RTPI. The cause of death was determined by the treating physician, a review of the medical records corroborated by the death certificate, or from the death certificate alone. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed using the log-rank test. Patients alive and disease free were censored. Univariable Cox regression models were used to assess the predictors of CSS after RN. Statistical significance was set at P .05. All reported P values are 2-sided. Statistical analysis was performed using SPSS statistics, version 20 (SPSS Inc, Chicago, IL).

Results

Patient and Tumor Characteristics The patient and tumor characteristics are listed in Table 1. RN was performed using a laparoscopic approach in 94 patients (49.5%) and

an open approach in the remainder. RCC was stage pT1 in 148 patients (77.9%) and low-grade (Fuhrman grade I-II) in 155 patients (81.6%). Most RCCs (82.1%) had a clear cell histotype. Coagulative necrosis was observed in 60 cases (31.6%) and sarcomatoid differentiation in only 1 case. Pathologic Assessment and Classification of RTPI Patterns A tumor pseudocapsule completely surrounded all the tumors and was a dense and continuous layer of connective tissue. RTPI was considered absent when the pseudocapsule was regular and continuous, with homogeneous thickness and an absence of tumor spikes (Figure 1A). Two main patterns of RTPI were defined: expansive RTPI (Figure 1B,C) and infiltrative RTPI (Figure 1D-H). Expansive RTPI was characterized by the presence of tumor cells that abutted the pseudocapsule, which, however, remained regular, well defined, and without breaks. In such cases, the pseudocapsule could be thinned (Figure 1B) or show undulations (Figure 1C). Infiltrative RTPI was characterized by the presence of tumor cells penetrating into the pseudocapsule with spikes that reached varying depths. Different variants of infiltrative RTPI could be described. These included as follows: a pseudocapsule of variable thickness with irregular undulations or erosions (Figure 1D); the presence of neoplastic spikes that penetrated the pseudocapsule perpendicularly without breaking it (Figure 1E); the presence of neoplastic spikes that penetrated the pseudocapsule horizontally without breaking it (Figure 1F); the presence of tumor cells almost completely penetrating the pseudocapsule (Figure 1G); and the presence of tumor cells completely penetrating the pseudocapsule (Figure 1H). Expansive or infiltrative RTPI using these defined histologic criteria was observed in 39.5% and 51.6% of the cases, respectively. Correlation of RTPI Patterns With Histologic Features The association between RTPI patterns and other histologic tumor variables in the present cohort is given in Table 2. No significant correlation was found between RTPI pattern and either pathologic tumor size or AJCC 2002 tumor stage. In contrast, a significant association was observed with Fuhrman grade (P ¼ .006). This association was also significant when a simplified Fuhrman classification system was used (low grade, Fuhrman I-II; high grade, Fuhrman III-IV; P ¼ .013). The RCC histologic subtype also correlated significantly with the RTPI pattern (P ¼ .034). Chromophobe RCCs appeared to be more likely to not invade the pseudocapsule, because 31.2% of these tumors showed no RTPI compared with 11.1% of papillary RCCs and 6.4% of clear cell RCCs. Survival Analysis The median postoperative follow-up period was 72 months (interquartile range [IQR], 39-108). At the last follow-up examination, 45 patients (23.7%) had died and 12 RCC-related deaths (6.3%) had occurred. The median follow-up period for the patients alive at the last follow-up visit was 77 months (IQR, 44-109). The 5- and 10-year CSS rates were 93.6%, 98.6%, and 100% and 84.9%, 91.5%, and 100% for patients with infiltrative, expansive, or no RTPI, respectively (Figure 2A). The patients with an infiltrative RTPI pattern had a significantly poorer CSS than that of patients without

this pattern of pseudocapsular invasion (P ¼ .039). The 5- and 10-year CSS rates were 93.6% and 84.9% for patients with infiltrative RTPI compared with 98.9% and 93% for those with expansive or no RTPI (Figure 3). No difference in overall survival was observed when stratified by RTPI pattern (P ¼ .34; Figure 2B). On univariable analysis, an infiltrative RTPI pattern (P ¼ .049), pathologic tumor size (P ¼ .005), pathologic tumor stage (pT2 vs. pT1; P ¼ .024), Fuhrman grade (III-IV vs. I-II; P ¼ .032), and coagulative necrosis (P ¼ .015) were significant predictors of cancerspecific death (Table 3).

Discussion

The diagnosis of renal tumors has been steadily increasing in recent years, with a parallel increase in the number of nephronsparing and radical surgeries performed. Despite timely and technically correct surgical treatment, a non-negligible proportion of organ-confined renal tumors will recur locally or progress to metastatic disease during the follow-up period.12 The postoperative surveillance strategies have been based mainly on tumor stage, which only reflects tumor size in organ-confined RCCs.13 An increasing knowledge of the prognosticators of oncologic outcomes after nephrectomy could support the definition of improved, tailored, postoperative surveillance protocols and the selection of patients at higher risk of recurrence for adjuvant treatment. Pathologic features such as nuclear grade, coagulative necrosis, and microvascular and collecting system invasion have already been found to have prognostic implications for organ-confined RCC.6 Some retrospective studies have also assessed the prognostic role of tumor invasion of the renal capsule overlying the exophytic part of renal tumors, with conflicting results.14-19 Although a pooled analysis of these reports revealed a poorer prognosis for patients with invasion of the renal capsule, these results were limited by the different inclusion criteria, sample size, and endpoints analyzed in the different studies.5 Tumor invasion of the pseudocapsule that completely surrounds renal neoplasms represents another potential prognostic factor for RCC.7 The renal capsule and tumor pseudocapsule are clearly different entities, although they can be difficult to differentiate on the perirenal tumor side. A tumor pseudocapsule surrounding renal neoplasm on both the parenchymal and the perirenal side has been described since the late 1940s.20,21 Recently, some investigators have evaluated the pseudocapsule in patients who underwent partial nephrectomy for renal tumors and confirmed the presence of a continuous, nonfenestrated, layer of dense connective fibrous tissue completely surrounding the tumor in 96% to 100% of cases.8,22 This fibrotic structure can be created by compression of the surrounding tissues by the tumor or by a reaction of these same tissues to the tumor itself. In the 1980s, Rosenthal et al23 and Rocca Rossetti et al24 first observed that RTPI was more frequent in lessdifferentiated renal tumors, suggesting it might

characterize organconfined renal tumors at greater risk of clinical progression. With careful analysis, different histologic patterns of pseudocapsular invasion can be observed and might indicate differing biologic and clinical tumor behavior. However, at present, no standardized classification of RTPI is available, and the prognostic role of different RTPI morphologic patterns has not been assessed. Our results have confirmed that a tumor pseudocapsule can be identified in all RCCs. Also, we have provided a thorough histologic classification of RTPI. We identified 2 main patterns of pseudocapsular invasion, defined as expansive and infiltrative RTPI. Expansive invasion is characterized by a protrusion of tumor cells into the pseudocapsule, which appears regularly or irregularly thinned or undulated. Infiltrative invasion is characterized by the perpendicular or horizontal growth of tumor cells at various depths through the pseudocapsule. We clearly described the different morphologic variants of each pattern with the aim of facilitating an accurate and reproducible diagnosis. The rate of RTPI reported in partial nephrectomy specimens has been 45% to 49% in published studies.7,8 According to our classification, some degree of RTPI will be present in a higher proportion of organ-confined renal tumors. This can be explained by the restriction of our analysis to RN specimens and, therefore, to larger tumors with potentially greater biologic aggressiveness and/or by the different criteria we used to define RTPI. The high prevalence of RTPI might represent a drawback for its application as a prognostic factor if one could not differentiate patterns with different prognostic impact. However, in our series, the expansive pattern of invasion—although associated with few cancer-specific deaths—appeared to characterize relatively indolent tumors that likely do not represent a significant oncologic threat. In contrast, tumors with an infiltrative RTPI pattern had a significant 4.38-fold greater risk of cancer-specific death compared with the other patients in our series. Our findings suggest that pathologists should thoroughly assess the tumor pseudocapsule on nephrectomy specimens to specifically investigate the presence of infiltrative RTPI, because it might indicate lesions at greater risk of progression that potentially need closer monitoring. The aggressive biology of tumors with infiltrative RTPI was further confirmed by the association of this pattern with a higher Fuhrman grade in our cohort. Indeed, 74.3% of high-grade tumors were characterized by infiltrative RTPI, while only 11.8% of tumors without RTPI harbored high-grade disease. Tumor histotype was also associated with RTPI, with chromophobe tumors less likely to present with an infiltrative pattern. In contrast, no association was observed between RTPI and tumor size and stage. A correlation with size and stage was instead consistently reported for invasion of the renal capsule,14,16,17,19 suggesting that these 2 histologic entities have different biologic value. The limitations of the present study included the relatively small sample size and the retrospective nature of the analysis. However, all the slides were reviewed by 2 expert genitourinary pathologists, and a standardized and

reproducible definition of RTPI patterns with their variants is provided. Furthermore, owing to the low number of cancer-related deaths in our low-stage population, a multivariable analysis could not be performed. Further studies on larger series are needed to confirm an independent prognostic role for RTPI in localized tumors. Such studies might also be able to assess the potential ability of morphologic variants of infiltrative and expansive RTPI to further discriminate prognosis. Finally, although the study was restricted to RN specimens, we believe the results can be extended to tumors removed by nephron-sparing surgery, which now represents the reference standard for the surgical treatment of localized renal tumors. However, additional studies are warranted to validate our classification in a series of partial nephrectomy specimens.

Conclusion

The presence of a fibrous pseudocapsule completely surrounding renal tumors was described decades ago; however, a standardized histologic definition and classification of RTPI patterns is not available. The present study has provided a detailed morphologic classification of RTPI, describing expansive and infiltrative patterns with their morphologic variants. The infiltrative pattern was more frequent in high-grade RCCs and was associated with a significantly greater risk of cancer-specific death, representing a potential marker of aggressive biology and, perhaps, metastatic potential in localized RCC considered at low risk of progression using current criteria. Therefore, an accurate pathologic assessment of RTPI in localized renal tumors appears potentially useful for identifying high-risk patients who require stricter follow-up strategies and who might be considered for adjuvant treatment in clinical trials. Further studies are needed to confirm our findings, validate our RTPI classification, and potentially support its integration with other pathologic and molecular features in prognostic nomograms for localized RCC.

Clinical Practice Points

- Limited information is available on the prognostic role of tumor invasion of the fibrous pseudocapsule that completely surrounds renal neoplasms.
- Different histologic variants of RTPI can be observed that might potentially predict different biologic and clinical behavior of RCC.
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A standardized histologic definition and classification of RTPI patterns is not currently available.

- We reviewed the pathologic slides and clinical information from a consecutive cohort of patients who had undergone RN for organ-confined RCC with the aim of better defining the histologic features of RTPI, describing the possible RTPI patterns, and assessing their correlation with other histologic features and prognosis.
- We identified 2 main patterns of pseudocapsular invasion: an expansive RTPI and an infiltrative RTPI, with specific histologic characteristics.
- A significant association of the patterns of pseudocapsular invasion with Fuhrman grade ($P = .006$) and RCC histologic subtype ($P = .034$) was detected.
- The expansive pattern of invasion, although associated with few cancer-specific deaths, appeared to characterize relatively indolent tumors that likely do not represent a significant oncologic threat.
- In contrast, tumors with an infiltrative RTPI pattern showed a significant 4.38-fold greater risk of cancer-specific death.
- Our findings suggest that pathologists should thoroughly assess the tumor pseudocapsule on nephrectomy specimens to specifically investigate the presence of infiltrative RTPI, because it can indicate lesions at higher risk of progression that potentially need closer monitoring.

Disclosure

The authors have stated that they have no conflicts of interests.

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